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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/782,899	02/23/2004	Minoru Fujimori	12381-002-999	5937

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EXAMINER
LONG, SCOTT

ART UNIT	PAPER NUMBER
1633	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/782,899	FUJIMORI ET AL.	
	Examiner	Art Unit	
	SCOTT LONG	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 December 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *47-51,53-64 and 73-79* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *47-51 and 58-64* is/are rejected.

7)☒ Claim(s) *53-57 and 73-79* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *12/22/2009*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 12/22/2008 has been entered.

Claim Status

Claims 47-51, 53-64, and 73-79 are pending. Claims 53-54 are amended. Claims 1-46, 52, and 65-72 are cancelled. Claims 73-79 are newly submitted. Claims 47-51, 53-64, and 73-79 are under current examination.

Priority

This application claims benefit as a Continuation of U.S. Application No. 09/816,391 filed 26 March 2001 (abandoned). The instant application also claims benefit from foreign application JAPAN 2000-287688 filed 12 September 2000. Therefore, the application has been granted the benefit date, 12 September 2000 from the foreign application, JAPAN 2000-287688.

RESPONSE TO ARGUMENTS

Claim Rejections - 35 USC § 112

The rejection of claim 52 under 35 USC 112, 2nd paragraph is withdrawn in response to the applicants claim amendments. The applicant's arguments have cancelled claim 52. Therefore, the rejection is moot. Therefore, the examiner hereby withdraws the rejection of claim 52 under 35 USC 112, 2nd paragraph.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or non-obviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of

the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 47-51 and 58-64 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Yazawa et al. (Proceedings of the American Association for Cancer Research Annual Meeting, Vol. 40, pp. 88, 1999) in view of Brown et al. (US2003/0103952) and further in view of Goshima et al. (Biochimie, 1990. vol.72: 207-214) and further in view of Claret et al. (J. Mol. Biol. 1997; 273: 93-104) for the reasons of record and the comments below.

The applicant's arguments have been fully considered but are unpersuasive.

The applicant has argued (Remarks, pages 7-11) that the cited art is not obvious over the claimed invention because the teachings of the cited art regarding the use of the HU promoter are insufficient. The applicant has divided his argument into several sections.

The applicant argues that Goshima does not teach an explicit sequence for the HU-promoter (referred to by Goshima as HB1) or its location in the genome of *Bifidobacterium longum*. The examiner agrees with this argument of the applicant. The applicant also argues that Goshima does not provide any disclosure whatsoever of the promoter(s) that regulate the sequence encoding HB1, or how HB1 protein might be

regulated. Additionally, the applicant argues that Goshima does not teach or suggest that HB1 is highly expressed in Bifidobacterium, relative to other Bifidobacterium proteins. Regarding these arguments, the examiner disagrees and interprets the teachings of Goshima differently that the manner in which the applicant does. The HU (HB1) protein is a histone-like protein that binds DNA in prokaryotes. Histones in eukaryotes, this protein is ubiquitously expressed and are considered to be housekeeping genes. Consequently, the HU promoter would seem a good choice for expression vectors, just as β-actin promoter is frequently used for constitutive expression of heterologous genes. Goshima et al. teaches that "HU protein has been well conserved in evolution of prokaryotes. In *E. coli* the intracellular concentration of HU protein is relatively high" (page 207, col.1, parag.2) and "HU-like protein…from *B.longum*…has similar properties to the HU protein in *E.coli*" (page 207, col.1, lines 8-10). Therefore, the examiner interprets the teachings of Goshima et al. to infer that the *B.longum* HU promoter is a housekeeping gene capable of expressing HU protein at a high concentration.

The applicant argues that Claret teaches the HU protein from *E. coli* is regulated by 4 different promoter (1 promoter for HU-1 subunit and 3 promoters for HU-2 subunit). The applicant seems to be arguing that the teachings of Claret suggest uncertainty about *B. longum* HU protein regulation. Goshima addresses the differences between the structures of *E. coli* and *B. longum* HU proteins; the *E. coli* HU protein consists of a heterodimer, while the B*. longum* HU protein consists of a homodimer made from monomers like the HU-1 subunit of the *E. coli* HU protein (Goshima, Introduction).

Since the HU-1 promoter of the *E. coli* HU protein is singular and is known to be highly conserved between prokaryotes, a skilled artisan would have every reason to believe the HU promoter of B*. longum* would be singular. The examiner concludes that there is little or no uncertainly about the singularity of the HU promoter of B*. longum.* There being a single HU promoter in B*. longum*, its activity would likely be active in a manner similar to that of the promoter for *E. coli* HU-1 subunit, at the beginning of log phase bacterial growth. Claret teaches "*hupA* gene, the first of the major *hup* mRNAs to be activated…starts early in the exponential growth phase" (page 100, col.2, Discussion). The applicant further argues "Claret does not teach or suggest that any of the *E. coli* HU promoters -- including the two promoters active during logarithmic growth --analyzed are "strong" promoters relative to any other *E. coli* promoters" (Remarks, page 10). Contrary to the applicant's assertion, Claret teaches the *E. coli* HU promoters are highly active during logarithmic growth and produce a very high percentage of the total mRNA transcripts produced during this phase. Figure 1B (page 95) shows the relative mRNA level produced by *hupA* is over 20% of total mRNA produced at its peak during logarithmic growth phase. In describing the method used to produce the data plotted on Fig. 1B, Claret states "RNA extraction and cDNA synthesis were performed….The relative RNA level of each product was calculated...relative to the sum of...all the products, and expressed as a percentage of the total specific RNA recorded during growth" (page 102, col.2, RNA measurements section). Since Claret also indicates that *hup* mRNA is unstable (page 94, col.2, last few lines), the very high level of mRNA transcripts of *hupA* (encoding HU-1 subunit) is due to a highly active promoter for HU-1

(homologous to *B. longum* HU). Therefore, the examiner finds the applicant's arguments unpersuasive.

The applicant concludes his arguments by suggesting that the HU promoter was non-obvious. The applicant argues multiple *Bifidobacterium* HU-like promoters might exist. The examiner cannot demonstrate or deny the possibility of such a suggestion, but based upon the teachings of Goshima and Claret, it seems that in all likelihood, there is a single promoter for the *Bifidobacterium* HU promoter. Goshima indicates that *Bifidobacterium* HU is encoded by a single gene, which shares homology to *E.coli* HU-1. Claret indicates that *E.coli* HU-1 is regulated by a single promoter. Therefore it would be most logical if *Bifidobacterium* HU is regulated by a single promoter. The applicant reiterates the arguments presented in the discussion of Claret, regarding the expression patterns of the different subunits of HU. As discussed above, the important teachings of the cited art indicate that *Bifidobacterium* HU is encoded by a single gene, which shares homology to *E.coli* HU-1 which is regulated by a single promoter. Therefore the "complexity" of gene regulation of *Bifidobacterium* HU, asserted by the applicant is not convincing to the examiner. Further, the applicant argues there is no nexus between Goshima and Claret, but offers nothing to substantiate this conclusory remark, other than a restatement of the arguments addressed above. Therefore, the examiner finds these arguments unpersuasive.

The applicant argues that the applicant applied hindsight reasoning to conclude a skilled artisan would have been motivated to apply the HU promoter for expression of heterologous proteins in *Bifidobacterium*. The examiner maintains that he has

established a prima face case of obviousness based upon the cited references. In addition to the evidence and arguments provided by the examiner, above and in the pending rejection, the instant specification states, "The HU gene (HU protein: histone-like DNA-binding protein, Biochimie, -72, 207 (1990)) known as a gene highly expressed in *B. longum* cells" (page 55, lines 4-6, emphasis added by examiner). According to MPEP 2128.02, A statement by an applicant in the specification or made during prosecution identifying the work of another as "prior art" is an admission which can be relied upon for both anticipation and obviousness determinations. The examiner interprets the teachings of the instant specification recited above as indicating that the state of the art recognized that "HU is highly expressed in *B. longum* cells." Since the art also recognized that the mRNA expression of HU is a large fraction of the total mRNA, it would be obvious to a skilled artisan that the HU promoter of *B. longum* is a promoter which could be used for highly expressing heterologous proteins. Accordingly, the examiner believes it is not hindsight reasoning and therefore finds the applicant's arguments unpersuasive.

Therefore, the examiner hereby maintains the rejection of claims 47-51 and 58-64 under 35 USC 103(a) as being unpatentable over Yazawa et al. in view of Brown et al. and further in view of Goshima et al. and further in view of Claret et al.

The examiner reiterates the pending rejection below:

Claims 47-51 and 58-64 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yazawa et al. (Proceedings of the American Association for Cancer Research Annual Meeting, Vol. 40, pp. 88, 1999) in view of Brown et al.

(US2003/0103952) and further in view of Goshima et al. (Biochimie, 1990. vol.72: 207-214) and further in view of Claret et al. (J. Mol. Biol. 1997; 273: 93-104).

Yazawa teaches using *Bifidobacterium longum* as a gene delivery vector for treating cancer in a buffer or solution, (that is, a pharmaceutical preparation). However, Yazawa does not specifically teach introducing a DNA coding for a protein having an activity of converting a precursor of an anti-tumor substance into the anti-tumor substance into a tumor using *Bifidobacterium longum*.

However, at the time the invention was made, introducing a DNA coding for a protein having an activity of converting a precursor of an anti-tumor substance into the anti-tumor substance into a tumor using a genetically modified bacterium was well known to one of ordinary skill in the art as exemplified by Brown (columns 1-26). Brown teaches using a genetically modified bacterium to deliver an enzyme to the hypoxic/necrotic environment of a tumor and systemically administering a pro-drug, which is converted at the site of the tumor to the toxic agent by the enzyme (columns 25-26). The enzyme/prodrug combination can be selected from following: nitroreductase/CB1954; cytosine deaminase/5-fluorocytosine; beta glucuronidase/ glucuronidated anticancer drugs (columns 5-6).

Neither Yazawa et al. nor Brown et al. teach utilizing the strong promoter, histone-like DNA binding protein (HU) promoter, in recombinant *Bifidobacterium longum* in order to express anti-tumor genes.

However, the HU promoter was known as in the art as a promoter which highly expresses HU protein in *E. coli* during logarithmic growth phase (Claret et al.). It was

further known in the art that the HU was highly conserved during evolution between *E.coli* and *Bifidobacterium longum* (Goshima et al.). However, utilizing the strong promoter, histone-like DNA binding protein (HU) promoter, in recombinant *Bifidobacterium longum* in order to express anti-tumor genes was not performed by any other researchers at the time of the filing. The examiner still believes that it is obvious to use *Bifidobacterium longum* as a vehicle for delivery of cancer therapeutics.

It would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to modify the teaching of Yazawa taken with Brown, Goshima and Claret, namely to use a genetically modified *Bifidobacterium longum* comprising a nucleic acid sequence encoding a protein having an activity of converting a precursor of an anti-tumor substance into the anti-tumor substance in a method to treat tumor tissues under anaerobic conditions and further using the HU promoter to express the anti-tumor substances.

One of ordinary skill in the art would have been motivated to introduce the DNA encoding a protein having an activity of converting a precursor of an anti-tumor substance into the anti-tumor substance into tumor tissues under anaerobic conditions using the genetically modified bacterium because the bacterium is a nonpathogenic anaerobic bacterium, which can selectively localize to solid tumors in an individual after systemic application and pro-drug cancer therapy was well known to one of ordinary skill in the art for treating tumor tissue.

In addition, it would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to modify the teaching of Yazawa taken with

Brown, namely to use any enzyme/prodrug combination in the method to treat tumor tissues under anaerobic conditions. One of ordinary skill in the art would have been motivated, as a matter of designer's choice, to use an enzyme/prodrug combination selected from following: nitroreductase/CB1954; cytosine deaminase/5-fluorocytosine; beta-glucuronidase/glucuronidated anticancer drugs because the enzyme/prodrug combinations were well known to one of ordinary skill in the art for treating hypoxic tumor tissue.

In addition, it would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to combine the teaching of Yazawa taken with Brown and Goshima and Claret, namely to use an expression vector that has a HU promoter and terminator that function in a Bifidobacterium. Furthermore, one of ordinary skill in the art would have been motivated to use the HU promoter in *B. longum* to express anticancer genes because Goshima, in particular, suggest *B.longum* could be used in the medical sciences.

One of ordinary skill in the art would have been motivated to use a histone-like binding protein promoter and terminator of Bifidobacterium because one of ordinary skill in the art understands that a promoter and a terminator are required for the vector to express the protein of interest. Furthermore, having a promoter which expresses an important protein such as those interacting with histones could provide high levels of expression of the anti-tumor substance.

Therefore the invention as a whole would have been *prima facie* obvious to one ordinary skill in the art at the time the invention was made.

Allowable Subject Matter

Claims 53-57 and 73-79 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

While the *B. longum* HU promoter was known to be highly expressive, it has not been isolated to the degree defined in the instant claims and plasmid. Prior to the claimed invention, large nucleic acids fragments comprising the *B. longum* HU promoter and terminator were submitted into the public record as part of the sequencing of the genome of *B. longum.* At the time the genomic sequencing was performed, the functions of these sequences were unknown.

Conclusion

No claims allowed.

Examiner Contact Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Scott Long** whose telephone number is **571-272-9048**. The examiner can normally be reached on Monday - Friday, 9am - 5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Joseph Woitach** can be reached on **571-272-0739**. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Scott Long/
Patent Examiner, Art Unit 1633